More than just side effects: the role of clinical and psychosocial factors in non-adherence to tamoxifen

Objectives: Tamoxifen non-adherence is apparent in up to half of breast cancer survivors and is associated with increased risk of recurrence and reduced quality of life. However, factors contributing to non-adherence in this population are currently poorly understood. This study explored the relationship between key components of the Common Sense Model of Illness Representations (CSM) / the Theory of Planned Behaviour (TPB) and intentional and unintentional non-adherence in a large sample of women prescribed tamoxifen following primary breast cancer.

Design: Cross-sectional questionnaire study (n=777).

Methods: Women were eligible if they were over 18, had been diagnosed with primary breast cancer and had been prescribed tamoxifen. Participants were recruited in clinic or online and completed questionnaires assessing illness perceptions, treatment beliefs, adherence, quality of life, social support, distress and the key TPB components. Logistic regressions were conducted to test elements from each model and to identify correlates of intentional and unintentional non-adherence.

Results: Patients were classified as non-adherent based on Medication Adherence Rating Scale scores. 44% of the population were non-adherent; 41% reported unintentional non-adherence and 9% reported intentional non-adherence. Study variables accounted for more variance in intentional (Nagelkerke R^2 = 46%) than unintentional non-adherence (Nagelkerke R^2=17%). Intentional non-adherence was best explained by a combination of TPB and CSM variables, but these variables did not contribute significantly to unintentional non-adherence.

Conclusions: The TPB and the CSM provide a useful framework for understanding intentional tamoxifen non-adherence. Elements from both models should be considered when designing interventions to increase adherence rates.

Introduction

Breast cancer is the most common cancer in women in the UK, and whilst survival rates are improving, it is still the second most common cause of cancer-related death in the UK (Cancer Research UK, 2014). About 75% of breast cancers are oestrogen receptor positive (ER+), which means the cancer cells are stimulated by oestrogen (Harrell et al., 2007). Adjuvant hormonal therapy (HT) such as tamoxifen is prescribed to women with ER+ breast cancer to reduce the risk of recurrence. Tamoxifen, which works by blocking the oestrogen receptor, reduces the risk of recurrence by 46% and the risk of mortality by 26% (Early Breast Cancer Trialists' Collaborative Group, 1998). It is prescribed for between five and ten years and is one of the most effective systemic therapies available for ER+ early breast cancer (Aguilar et al., 2010).

Treatment adherence, defined as the extent to which patients take their medication as prescribed (Sabate, 2003), is often not considered to be an issue with cancer patients, due to the life threatening nature of the illness (Wu, Stafkey-Mailey, & Bennett, 2012). However, despite the clear clinical benefits of tamoxifen, many patients either stop taking their medication early or do not take the full dosage. Non-adherence ranges from 6% - 55% (Ayres, Baldoni, Borges, & Leira Pereira, 2014; Hershman et al., 2011; McCowan, Wang, Thompson, Makubate, & Petrie, 2013) and rises over time (Hershman et al., 2010; Partridge, Wang, Winer, & Avorn, 2003). This variability in adherence rates is likely due to variations in study design and populations, such as different healthcare and cultural contexts. Furthermore, there is significant variability in the tools used to assess adherence, with studies utilizing self-report measures reporting higher rates of adherence (Moon et al., 2017). A further 50% of patients completely discontinue tamoxifen within five years (Kostev et al., 2013; van Herk-Sukel et al., 2010), which is known as non-persistence. Non-adherence and non-persistence to tamoxifen are associated with increased risk of death and early recurrence (Barron, Cahir, Sharp, & Bennett, 2013; Hershman et al., 2011; Makubate, Donnan, Dewar, Thompson, & McCowan, 2013), as well as fewer quality adjusted life years and increased medical costs (McCowan et al., 2013). This indicates a need to understand why women are not adhering, so we can intervene to increase adherence rates and improve clinical outcomes. Identifying psychosocial predictors of non-adherence is essential in the development of interventions, as these factors have the potential to be modified. For example, medication beliefs and perceived control over medication taking are associated with medication adherence in a range of conditions (Conner, Black & Stratton, 1998; Horne & Weinman, 1999) and have been successfully targeted in interventions (Petrie et al., 2012; Sheeran & Orbell, 2000). However, evidence on modifiable psychological predictors of tamoxifen adherence is currently lacking (Moon, Moss-Morris, Hunter, Carlisle, & Hughes, 2017; Murphy, Bartholomew, Carpentier, Bluethmann, & Vernon, 2012), with an emphasis in the literature on non-modifiable clinical and demographic factors.

Non-adherence can be conceptualised as intentional, where the patient makes a deliberate decision not to adhere, or unintentional, where they may forget or not understand the instructions. Unintentional non-adherence is more prevalent in breast cancer, however this may be due to forgetting being more socially acceptable and therefore more frequently reported (Atkins & Fallowfield, 2006; Unni & Farris, 2011). Some studies suggest that unintentional non-adherence may be related to medication beliefs (Gadkari & McHorney, 2012; Schüz et al., 2011), which questions how unintentional these behaviours are. However, recent studies in breast cancer have supported the idea of a distinction between unintentional and intentional non-adherence (Kimmick et al., 2015; Wouters et al., 2014). Understanding these different types of non-adherence and the associated predictors would be useful in tailoring interventions to improve adherence.

Tamoxifen is associated with side-effects, including hot flushes, vaginal dryness and low mood, which are often assumed to drive non-adherence. However, the relationship between side-effects and non-adherence is inconsistent (Moon et al., 2017). Whilst a recent systematic review has found some evidence for potentially modifiable psychosocial correlates of HT non-adherence, including self-efficacy for medication taking, medication beliefs and social support (Moon et al., 2017), previous research has largely failed to use theoretical models when investigating non-adherence. Theory provides a structured framework for investigating key determinants of non-adherence and helps with intervention development (Holmes, Hughes, & Morrison, 2014). This study will use two popular models of health behaviour to investigate tamoxifen non-adherence; the Common Sense Model (CSM) and the Theory of Planned Behaviour (TPB). These models have been used extensively to predict health behaviours, but to the best of our knowledge, no peer reviewed research has applied them to tamoxifen adherence.

The TPB proposes that adherence is driven by intentions to engage with treatment, which are in turn influenced by subjective norms, attitudes and perceived behavioural control (PBC), which also exerts a direct influence over behaviour (Ajzen, 1991). Previous studies have supported the TPB as a framework for understanding non-adherence (Kagee & Van der Merwe, 2006) with key TPB variables explaining large proportions of variance in medication adherence (Bane, Hughe, & McElnay, 2010; Conner et al., 1998). The CSM proposes that patients hold illness representations, or implicit common sense beliefs about their illness, which are used as a framework for making sense of and coping with an illness (Leventhal, Diefenbach, & Leventhal, 1992). Key illness perceptions are identity (the label given to the illness and symptoms experienced), causal beliefs, timeline beliefs, treatment control, personal control and consequences. Patients also hold emotional representations of their illness. These illness perceptions have been associated with adherence in several studies, highlighting the utility of the CSM as a framework for investigating non-adherence (Brewer, Chapman, Brownlee, & Leventhal, 2002; Patel & Taylor, 2002; Ross, Walker, & MacLeod, 2004). The CSM is a dynamic model where illness perceptions affect selection of coping strategies, and the

outcome of these coping strategies affects illness perceptions. The explanatory power of the CSM has been improved by the addition of medication beliefs, which may act as a more proximal determinant of non-adherence. These medication beliefs include concerns, and necessity beliefs, which relate to how necessary the patient feels the medication is for their current and future health. Necessity and concern beliefs are stronger predictors of adherence than clinical or demographic factors (Horne & Weinman, 1999). The differential between necessity and concern beliefs is often used to predict non-adherence and represents a cost-benefit analysis patients may undergo before making decisions about treatment (Horne & Weinman, 1999; Wileman et al., 2011). This framework also includes more general beliefs about medication, but the specific beliefs (necessity/concerns) have been shown to be more important in relation to medication adherence (Grunfeld et al., 2005; Horne & Weinman, 1999; Zwikker et al., 2014a).

The primary aim of this study was to explore the relationship between key aspects of the CSM and TPB and both intentional and unintentional non-adherence, in order to facilitate the development of interventions to improve adherence. Elements from both models were included to heighten the explanatory power and to explore both perceptions around cancer survivorship (CSM) and the medication taking behaviour itself (TPB), as it was felt that both these sets of variables may have an influence on non-adherence. Testing both models concurrently allows for a broader range of predictor variables to be tested, and may allow for creation of a more parsiminous model. Demographic, clinical and other psychosocial variables such as distress and social support were controlled for in the analysis as they have previously shown associations with tamoxifen non-adherence (Moon et al., 2017). Based on previous research, we hypothesise that unintentional non-adherence will be reported more frequently than intentional non-adherence, and that psychological variables from the CSM andTPB, such as necessity and concern beliefs, will be related more to intentional than unintentional non-adherence.

As adherence rates fall across time (Nekhlyudov, Li, Ross-Degnan, & Wagner; Schover, Baum, Fuson, Brewster, & Melhem-Bertrandt, 2014), a secondary aim was to investigate whether adherence was higher in women who were nearer the beginning of treatment. Differences in CSM and TPB variables between women within six months of treatment and women who are later on in treatment were also explored, to provide understanding of how illness or treatment beliefs differ across the treatment trajectory. Little is currently known about the illness beliefs held by these patients or how they may change over time.

Method

Participants and procedure

The study was approved by the Northampton National Research Ethics Committee (REF 14/EM/1207). Women were eligible for the study if they were over 18, had been diagnosed with

primary breast cancer and had been prescribed tamoxifen. Patients were recruited through 27 oncology clinics across England and through online advertisements. In clinic, eligible women were identified by clinic staff and were told about the research during their appointment. Patients were given an information sheet and consent form as well as verbal information about the study. They could complete the questionnaire in clinic, take it away and return it using a stamped addressed envelope, or complete it online. Informed consent was taken from all participants. Some patients were recruited through a postal invitation sent out by clinic staff to eligible patients. Online advertisements were placed on patient support websites and Facebook groups. When a participant saw this advertisement, they contacted the researcher who gave them information about the study and screened them for eligibility. They were then either posted the questionnaire or given a link to complete it online. The questionnaire took between 20 – 30 minutes to complete.

Measures

Sociodemographic and clinical variables

Participants provided data on demographic (age, ethnicity, relationship status, employment status, age left full time education, menopausal status at diagnosis), clinical (breast cancer stage, previous treatment, comorbidities) and treatment related factors (date prescribed tamoxifen, duration of tamoxifen treatment, type of prescribing clinician).

Social Support

Social support was measured using the Multidimensional Scale of Perceived Social Support (Zimet, Dahlem, Zimet, & Farley, 1988). Each item was scored on a seven point scale, with higher scores indicating higher levels of support. The scale has demonstrated good internal and test-retest reliability and has been used successfully to measure social support in patients with breast cancer (Oztunc, Yesil, Paydas, & Erdogan, 2013). Internal consistency in the current study was 0.96.

Distress

Distress, measured using The Hospital Anxiety and Depression Scale (HADS), was included as a covariate (Zigmond & Snaith, 1983). The scale includes seven items measuring depression and seven measuring anxiety. Following recent recommendations, the scale was used as a measure of general distress (Norton, Cosco, Doyle, Done, & Sacker, 2013). The scale showed good reliabity in the current study (α=.91).

Side effects

The FACT-ES is a quality of life scale for patients with breast cancer taking HT (Fallowfield, Leaity, Howell, Benson, & Cella, 1999). The additional concerns subscale was used to measure side-effects. Patients provide an answer on a five point scale from ‘not at all’ to ‘very much’ to indicate

how much they have experienced each side-effect for a list of 18 side effects. This provides a combined measure of both number and intensity of side-effects, representing the overall level of bother from side effects. The subscale showed good reliability in the current study (α =.87).

Information about treatment

To assess how informed patients are about their treatment, they were asked the extent to which they agreed or disagreed with four statements, such as "I feel confident in my understanding of how tamoxifen helps me". The scale showed good reliability (α =.89) in the current study.

Illness representations

The IPQ-BCS (Moon, Moss-Morris, Hunter, & Hughes, 2017), a modified version of the Revised Illness Perceptions Questionnaire, was used to measure components of the CSM. The scale has good psychometric properties and includes ten subscales; cure, risk of recurrence, tamoxifen consequences, breast cancer consequences, personal control, treatment control, illness coherence, emotional representations, tamoxifen identity and causes of recurrence. The subscales have previously demonstrated good internal reliability with Cronbach's alphas ranging from .76 to .92. Each scale includes four items scored on a 5-point Likert-type scale, with the exception of the tamoxifen identity and causes of recurrence scales. The identity scale includes a list of symptoms where participants indicate if they have experienced each symptom and if they attribute it to their tamoxifen treatment. The scale is scored by summing the number of symptoms attributed to tamoxifen. The causes of recurrence scale includes 14 possible causes. A previous exploratory factor analysis has indicated two factors for causes; psychological attributions (e.g. *my emotional state*) and health behaviours (e.g. *diet or eating habits)* (Moon et al., 2017).

Beliefs about Medicines

Beliefs about Medicines were measured as part of the extended CSM, which has particular relevance for medication adherence. The BMQ-Specific was used to measure beliefs regarding the necessity of taking tamoxifen and concerns about adverse effects. The scale has previously shown good psychometric properties (Horne, Weinman, & Hankins, 1999). A differential score was calculated by taking the total score for concerns away from the total score for necessity beliefs, as recommended by the authors of the BMQ (Horne & Weinman, 1999). A positive differential suggests that the necessity beliefs outweigh the concerns.

Theory of Planned Behaviour

Items relating to TPB variables were developed following guidelines from Francis et al. (2004) and Ajzen (2002). Subscales include intention to take tamoxifen, subjective norms, attitude and PBC. Intention, subjective norm and PBC were measured on a 7-point Likert scale. Attitudes were measured with five semantic differential scales scored on a ten point scale. Each subscale showed

good reliability in the current study (α= 0.67 – 0.82), with the exception of subjective norms (α= 0.52), however all subscales were included in order to fully test the model.

Adherence

The Medication Adherence Report Scale (MARS; Horne, Hankins, & Jenkins, 2001) includes five statements about taking medication, which are each scored on a five point scale from never to always. The scale attempts to avoid any issues regarding social desirability by asking questions in a non-threatening and non-judgemental way. The scale has demonstrated good internal reliability and test-retest reliability and has been used multiple times in breast cancer patients (Boonstra et al., 2013). Scores on the MARS were strongly positively skewed and therefore the data was dichotomised based on recommendations from previous papers (de Vries et al., 2014). The MARS includes a one item sub-scale on unintentional non-adherence (total score of 5) and a four item sub-scale on intentional non-adherence (total score of 20), with a total possible overall adherence score of 25. On the basis of previous studies, participants were classed as unintentionally non-adherent if they scored below 5 and intentionally non-adherent if they scored below 20 on the respective sub-scales (Daleboudt et al., 2011; Timmers et al., 2014; de Vries et al., 2014). Participants could be classed as both intentionally and unintentionally non-adherent.

Statistical analysis

Relationships between hypothesized correlates and intentional/unintentional non-adherence were tested using Cramer's V for categorical variables and biserial correlations for continuous variables. Separate multiple logistic regressions were carried out to assess the relationships between intentional and unintentional non-adherence and components of the CSM and TPB. Clinical, demographic and potentially confounding psychosocial variables which showed a significant bivariate relationship with non-adherence were entered into the first step of the regression models. The CSM and TPB components were entered into the next step, to assess their impact on adherence after the demographic variables have been taken into account. The ability of components from each model to explain non-adherence was assessed using Nagelkerke R^2 (pseudo R^2) to measure the proportion of variance explained. Model fit was also assessed by the -2 Log Liklihood statistic (-2LL). Lower -2LL values indicate superior model fit, and therefore if the addition of variables reduces the -2LL value, the variables have improved the model fit. The reduction in the -2LL statistic for each step is represented by chi-squared. T-tests using Bonferroni correction were used to compare women in their first year of treatment to women who were later on in treatment.

Results

Demographics of sample

1246 women were invited to participate from clinics and 758 women completed the questionnaire (61% response rate). An additional 60 women were recruited through online advertising. Forty-one (5%) women reported having discontinued tamoxifen and were removed from the sample. The final sample included 777 women. All participants were female, had Stage I-III breast cancer and had been prescribed tamoxifen (Table 1). The mean age was 53 (SD=10, range 30-90). Participants were mostly White British (86%), married (58%) and employed (65%). Just under half of patients had been prescribed tamoxifen less than one year ago, 22% 1-2 years ago and 31% over two years ago. Two thirds of participants self-reported being premenopausal or menopausal at time of diagnosis.

Adherence rates

Non-adherence was rated using cut-offs on the MARS. 44% (n=340) showed any sign of non-adherence, 9% (n=71) reported intentional non-adherence and 41% (n=321) reported unintentional non-adherence.

Explanatory variables

Means and SDs for each subscale are shown in Table 2. Mean anxiety levels (6.9, SD=4.4) were higher than depression rates (4.1, SD=3.8) but both were within normal ranges for the general population. The mean distress score was 11.0 (SD=7.5). Participants had relatively high beliefs in treatment control (mean=15.3, SD=2.5), illness coherence (mean=15.4, SD=2.9) and cure (mean=15.7, SD=3.0). An average of 5.6 symptoms were attributed to tamoxifen (SD=4.9). BMQ differentials were slightly above 0, showing that on average, participants had positive necessity-concern differentials (2.1, SD=5.2). Mean scores for intentions (6.5, SD=1.2), subjective norm (6.0, SD=1.0) and PBC (6.2, SD=1.0) were all high and attitudes were positive (7.9, SD=1.7).

Intentional non-adherence

The only demographic or clinical variables associated with intentional non-adherence were previously having a double mastectomy (Cramer's V=.10, p=.01) and months since prescribed tamoxifen (r_b=.17, p=.01) (See supplementary material, Appendix E). Side-effect intensity (r_b=.44, p<.001), distress (r_b=.37, p<.001), social support (r_b =-.19, p=.013) and how informed participants were (r_b=-.13, p=.030) were also associated with intentional non-adherence and were entered into the first step of the model.

Table 1. Participant demographics.

Characteristic	N (%)
Age	30 – 90 Mean: 53 (SD: 10)
Ethnicity	666 (86%) White British
	110 (14%) Other
Relationship status	555 (72%) With partner
	218 (28%) Separated /Divorced /Single/Widowed
Job status	504 (65%) Employed full time / part time
	209 (28%) Retired / Homemaker / Other
	61 (8%) Unemployed
Time since prescribed tamoxifen	< 6 months: 206 (28%)
	6 – 12 months: 142 (19%)
	1 – 2 years: 162 (22%)
	2 – 3 years: 99 (13%)
	3 – 4 years: 61 (8%)
	>4 years: 75 (10%)
Stage at diagnosis	Stage I: 308 (40%)
	Stage II: 326 (43%)
	Stage III: 93 (12%)
	Unsure: 35 (5%)
	Missing: 14 (2%)
Menopausal status at diagnosis	Pre-menopausal/menopausal: 511 (67%)
	Post-menopausal: 212 (28%)
	Unsure: 35 (5%)
	Missing: 18 (2%)
Previous treatment	Lumpectomy: 63%
	Single Mastectomy: 34%
	Double Mastectomy: 6%
	Chemotherapy: 51%
	Radiotherapy: 73%
Tamoxifen duration	One or two years: 16 (2%)
	Five years: 496 (64%)
	Ten years: 190 (25%)
	For life: 1 (0.1%)
	Unsure: 40 (5%)
	Missing: 26 (3%)
Healthcare professional who prescribed tamoxifen	Oncologist: 595 (77%)
	Surgeon: 130 (17%)
	Nurse: 24 (3%)
	GP: 5 (1%)
	Unsure / missing: 23 (2%)

Table 2. Relationship between explanatory variables and non-adherence

	Mean (SD)	Range	Correlation with intentional non-adherence	Correlation with unintentional non-adherence
Necessity/concerns differential	2.10 (5.23)	-20 - 20	-0.44***	-0.18***
Tamoxifen consequences	10.06 (4.09)	4 – 20	0.49***	0.12**
Breast cancer consequences	12.11 (3.71)	4 – 20	0.21***	0.07
Risk of recurrence	10.48 (3.45)	4 – 20	0.00	0.04
Cure	15.66 (3.04)	4 – 20	-0.08	0.04
Personal control	13.73 (3.01)	4 - 20	-0.07	0.09
Treatment control	15.32 (2.46)	6 - 20	-0.09	0.02
Coherence	15.38 (2.86)	4 - 20	-0.06	0.01
Emotional representations	13.23 (4.30)	4 - 20	0.08	0.07
Attributing side effects to tamoxifen	5.75 (4.87)	0 – 22	0.38***	0.19***
Cause: psychological attributions	9.52 (2.87)	3 - 15	0.23***	0.09
Cause: health factors	13.15 (2.99)	4 - 20	-0.03	0.10*
Attitude	7.86 (1.66)	1 – 10	-0.35***	0.14**
Intention	6.46 (1.18)	1 -7	-0.69***	0.22***
Subjective norm	6.03 (1.03)	1 – 7	-0.19**	0.14**
Perceived behavioural control	6.18 (1.02)	1-7	-0.70***	0.22***

*** p≤.001, **p<.01, *p<.05

CSM components associated with intentional non-adherence in the bivariate analysis were; BMQ differential, tamoxifen consequences, breast cancer consequences, cause: psychological attributions and tamoxifen identity. From the TPB; intention, subjective norm and attitude were all associated with intentional non-adherence (Table 2). Two logistic regressions were conducted to test separately the measured components of the CSM and TPB and a third regression combined the CSM and TPB variables. The model combining both the CSM and TPB variables explained the most variance in intentional non-adherence (Nagelkerke R^2=46%) (Table 3). In this model, the variables in Step 1 explained 20% of the variance ($\chi^2(5) = 60.06$, p<.001, R^2=20%). Higher levels of distress (OR=1.06, 95% CI=1.02-1.11) and higher intensity of side-effects (OR=1.05, 95% CI=1.03-1.08), having a double mastectomy (OR=3.18, 95% CI=1.33-7.60) and a longer duration of tamoxifen prescription (OR=1.01, 95% CI=1.00-1.02) were associated with increased odds of intentional non-adherence.

Table 3. Multiple logistic regressions to predict intentional non-adherence

	CSM (n=658)		TPB (n=652)		Combined model (n=611)	
	OR	95% CI	OR	95% CI	OR	95% CI
Step 1						
Side effect intensity	1.02	0.99 – 1.05	1.03	1.00 – 1.06	1.01	0.98 – 1.05
Social support	0.99	0.76 – 1.28	1.01	0.77 – 1.31	0.94	0.70 – 1.26
Extent patients feel informed about tamoxifen	0.95	0.87 – 1.05	1.01	0.91 – 1.11	1.03	0.91 – 1.15
Distress	1.04	0.99 – 1.09	1.03	0.98 – 1.09	1.05	0.99 – 1.12
Months since prescribed	1.01	0.99 – 1.03	1.01	0.99 – 1.02	1.01	0.99 – 1.03
Double Mastectomy (received)	3.55	1.37 – 9.18	5.35	2.07 – 13.88	6.41	2.26 – 18.19
Step 2						
Necessity/concerns differential	0.89	0.83 – 0.95			0.97	0.89 – 1.06
Tamoxifen consequences	1.15	1.04 – 1.27			1.06	0.94 – 1.19
Breast cancer consequences	0.96	0.87 – 1.08			0.93	0.81 – 1.05
Risk of recurrence	0.88	0.80 – 0.97			0.87	0.76 – 0.98
Cure	0.94	0.84 – 1.06			0.96	0.84 – 1.10
Personal control	0.93	0.81 – 1.05			0.97	0.85 – 1.12
Treatment control	1.10	0.92 – 1.23			1.05	0.86 – 1.28
Coherence	1.02	0.91 – 1.17			1.01	0.87 – 1.16
Emotional representations	0.93	0.86 – 1.03			0.96	0.86 – 1.07
Attribution of symptoms to tamoxifen	1.03	0.95 – 1.09			1.05	0.96 – 1.14
Cause: psychological attributions	2.06	1.34 – 3.05			2.28	1.40 – 3.71
Cause: health behaviours	0.58	0.40 – 1.01			0.41	0.24 – 0.72
Attitude			1.15	0.90 – 1.47	1.29	0.98 – 1.70
Intention			0.69	0.53 – 0.89	0.72	0.53 – 0.98
Subjective norm			1.19	0.86 – 1.63	1.11	0.78 – 1.58
Perceived behavioural control			0.43	0.30 – 0.62	0.37	0.24 – 0.56
	Step 1 -2LL: 353.3 Step 1 R^2 = .19 Step 1 $\chi2$ = 62.1 (p<.001) Step 2 –2LL: 302.79 Step 2 R^2 = .34 Step 2 $\Delta\chi2$ (12) = 50.52 (p<.001)		Step 2 –2LL: 279.9 Step 2 R^2 = .39 Step 2 $\Delta\chi2$ (4) = 64.4 (p=.000)		Step 1 -2LL: 332.3 Step 1 R^2 = .20 Step 1 $\chi2$ =60.06 (p<.001) Step 2 –2LL: 243.1 Step 2 R^2 = .46 Step 2 $\Delta\chi2$ (16) = 89.4 (p=.000)	

Adding the CSM and TPB variables significantly improved the model fit and explained a further 26% of the variance ($\Delta\chi^2(16) = 89.4$, p<.001, R^2=46%). After adding these variables, the only variable in step 1 still significantly associated with non-adherence was double mastectomy (OR=6.41, 95% CI=2.26-18.20). In terms of CSM variables, stronger beliefs in the risk of recurrence (OR=0.87,95%

CI=0.76-0.98) and stronger beliefs that health behaviours cause a recurrence were associated with decreased odds of non-adherence (OR=0.41, 95% CI=0.24-0.72), whereas beliefs that stress caused a recurrence were associated with two-fold increased odds of non-adherence (OR=2.28, 95% CI =1.40 – 3.71). Higher levels of PBC (OR=0.37, 95% CI=0.24-0.56) and intention (OR=0.73, 95% CI=0.52-0.98) were associated with decreased odds of intentional non-adherence.

Unintentional non-adherence

Individual associations between adherence and variables were tested using Cramer's *V* and biserial correlations. There were small but significant relationships between unintentional non-adherence and ethnicity (Cramer's *V* =.09, p=.007), relationship status (Cramer's *V*=.13, p=.007) and menopausal status (Cramer's *V*=.15, p =.001). There was a moderate relationship between job status and unintentional non-adherence (Cramer's *V*=.22, p<.001) and a weak relationship between previous chemotherapy and unintentional non-adherence (Cramer's *V*=.08, p=.038) (See supplementary material). Age (r_b=.22, p<.001), age left full time education (r_b=.12, p=.006), side-effect intensity (r_b=.14, p<.001), social support (r_b=-.14, p=.007) and months since prescribed (r_b=.21, p<.001) were correlated with unintentional non-adherence. In terms of variables from the CSM, unintentional non-adherence was associated with; necessity/concerns differential, tamoxifen consequences, tamoxifen identity and cause: health behaviours. TPB variables associated with unintentional non-adherence in the bivariate analysis were PBC, intention, subjective norm and attitudes (Table 2).
Separate logistic regressions were carried out to test the measured components of the CSM, the TPB and then a combination of CSM and TPB variables. The model including the CSM variables and the model including a combination of CSM and TPB variables both explained 17% of the variance in unintentional non-adherence (Table 4). Control variables were entered in step one, explaining 13% of the variance in unintentional non-adherence ($\Delta\chi^2(10) = 53.1$, p<.001, R^2=13%). Women who were white (OR=0.48, 95% CI=0.24-0.99) or older (OR=0.97, 95% CI=0.94-0.99) had lower odds of non-adherence and women who were employed (OR=2.08, 95% CI=1.32-3.30) or had been taking tamoxifen longer (OR=1.02, 95% CI=1.01-1.03) had higher odds of non-adherence. Adding variables from the CSM/TPB in the second step of the model explained a further 4% of variance, but did not significantly improve the model fit.

Table 4. Multiple logistic regressions to predict unintentional non-adherence

	CSM (n=575)		TPB (n=574)		Combined model (n=535)	
	OR	95% CI	OR	95% CI	OR	95% CI
Step 1						
Side effect intensity	1.01	0.99-1.03	1.01	0.99-1.02	1.00	0.98-1.03
Social support	0.88	0.75-1.02	0.91	0.79-1.06	0.89	0.76-1.03
Ethnicity (white)	0.43	0.21-0.88	0.53	0.26-1.07	0.43	0.20-0.91
Age	0.96	0.93-0.99	0.97	0.95-1.00	0.97	0.94-1.00
Relationship status (with partner)	0.73	0.47-1.11	0.77	0.51-1.17	0.74	0.48-1.16
Employment status (employed)	2.16	1.37-3.38	2.12	1.95-3.33	2.10	1.30-3.39
Months since prescribed	1.02	1.01-1.03	1.02	1.01-1.03	1.02	1.01-1.03
Chemotherapy (received)	0.99	0.66-1.50	0.93	0.63-1.39	1.01	0.66-1.54
Age left full time education	0.99	0.93-1.05	1.02	0.96-1.08	0.98	0.92-1.05
Menopausal status (premenopausal)	0.66	0.40-7.09	0.83	0.51-1.34	0.69	0.38-1.10
Step 2						
Necessity/concerns differential	0.96	0.93-1.00			0.97	0.93-1.02
Tamoxifen consequences	1.00	0.94-1.07			0.98	0.92-1.05
Breast cancer consequences	0.98	0.92-1.05			0.97	0.91-1.04
Risk of recurrence	0.98	0.92-1.05			0.98	0.91-1.05
Cure	1.01	0.95-1.09			1.03	0.96-1.11
Personal control	1.01	0.93-1.10			1.03	0.95-1.12
Treatment control	1.04	0.94-1.16			1.03	0.92-1.15
Coherence	1.02	0.94-1.09			1.04	0.96-1.12
Emotional representations	1.01	0.96-1.07			1.02	0.96-1.08
Symptoms attributed to tamoxifen	1.03	0.98-1.08			1.03	0.98-1.09
Cause: psychological stress	1.04	0.82-1.31			1.08	0.85-1.38
Cause: health behaviours	1.21	0.89-1.63			1.07	0.78-1.46
Attitude			0.95	0.84-1.08	0.96	0.84-1.10
Intention			1.01	0.82-1.25	1.03	0.82-1.28
Subjective norm			0.95	0.79-1.15	0.99	0.80-1.21
Perceived behavioural control			0.80	0.63-1.02	0.78	0.60-1.01
	Step 1 -2LL: 719.4 Step 1 R^2 = .15 Step 1 $\chi2$ (10) = 65.65 (p<.001) Step 2 –2LL: 706.9 Step 2 R^2 = .17 Step 2 $\Delta\chi2$ (12) = 12.5 (p=.405)		Step 1 -2LL: 729.0 Step 1 R^2 = .13 Step 1 $\chi2$ (10) = 56.1 (p<.001) Step 2 –2LL: 721.4 Step 2 R^2 = .14 Step 2 $\Delta\chi2$ (4) = 7.6 (p=.108)		Step 1 -2LL: 680.1 Step 1 R^2 = .13 Step 1 $\chi2$ (10) = 53.1 (p<.001) Step 2 –2LL: 662.3 Step 2 R^2 = .17 Step 2 $\Delta\chi2$ (16) = 17.9 (p=.331)	

Adherence rates and perceptions in newly prescribed patients

Compared to women not in their first six months since prescription, women in their first six months of tamoxifen prescription reported lower levels of distress (t(427)=-3.04, p=.003) and less intense side-effects (t(427) = -6.76, p=<.001) (Table 5). They also had higher intentions to take tamoxifen (t(627)=2.36, p=.003) and a more favourable attitude towards tamoxifen (t(663)=2.20, p=.028). With regards to illness/treatment beliefs, women within six months of prescription had lower scores on tamoxifen consequences (t(743) = -4.33, p=<.001), attributed fewer symptoms to tamoxifen (t(489)= 5.94, p=<.001) and were less likely to believe they were cured (t(316) = -3.36, p=.001). Women in their first six months of treatment also had significantly higher overall adherence rates (t(743) =-2.33, p=.020). However, adherence scores and attitudes were no longer significantly different after Bonferroni correction.

Table 5. Descriptive statistics and t-tests to compare women in their first six months of treatment to women later on in treatment

	Women in their first six months of treatment (n=206) (range 1 – 6 months) *Mean (SD)*	Women not in their first six months of treatment (n=539) (range 6 months – 8 years) *Mean (SD)*	p value
MARS scores	24.34 (1.44)	24.01 (1.76)	.020
Necessity/concerns differential	2.50 (5.36)	1.98 (5.24)	.233
Tamoxifen consequences	9.09 (3.56)	10.45 (4.26)	<.001*
Breast cancer consequences	12.33 (3.59)	12.03 (3.80)	.338
Risk of recurrence	10.41 (3.41)	10.52 (3.51)	.703
Cure	15.01 (3.41)	15.92 (2.84)	.001*
Personal control	13.59 (3.16)	13.82 (2.98)	.366
Treatment control	15.41 (2.49)	15.34 (2.42)	.722
Coherence	15.14 (2.98)	15.53 (2.78)	.099
Emotional representations	13.27 (4.20)	13.28 (4.33)	.982
Attributing side effects to tamoxifen	4.36 (3.79)	6.41 (5.09)	<.001*
Attitude	8.09 (1.45)	7.78 (1.71)	.028
Intention	6.63 (0.75)	6.41 (1.28)	.003*
Subjective norm	6.12 (0.98)	5.98 (1.04)	.097
Perceived behavioural control	6.28 (0.90)	6.14 (1.07)	0.73
Distress	23.73 (6.70)	25.48 (7.78)	.003*
Side effect intensity	35.11 (11.23)	41.62 (13.03)	<.001*

* Relationship remained significant after Bonferroni correction.

Discussion

This study explored associations between key components of the CSM and TPB with intentional and unintentional tamoxifen non-adherence. This is one of the largest studies to date to investigate psychosocial correlates of tamoxifen non-adherence and to use validated models of health behaviour as a framework. Results showed that key elements from both theories provide a useful framework for investigating intentional non-adherence. Drawing key variables from both the CSM and TPB provided the best explanation of intentional non-adherence, but these variables were not able to improve the explanation of unintentional non-adherence over and above clinical and demographic factors. Just under half of the sample were found to be non-adherent, with much higher percentages for unintentional than intentional non-adherence, as hypothesised. The figure of around 44% non-adherence has been found in many other studies of HT non-adherence (Kimmick, Camacho, Hwang, & Anderson, 2009; Lee et al., 2014; Seneviratne et al., 2015). Other studies have also supported the finding of higher rates of unintentional rather than intentional non-adherence (Kimmick et al., 2015; Tinari et al., 2015; Wouters et al., 2014). However, it is currently unclear if this reflects truly higher rates or the fact that forgetting may be more socially acceptable and is therefore endorsed more frequently by respondents (Atkins & Fallowfield, 2006). The current study identified unique correlates of intentional and unintentional non-adherence, and found poor prediction of unintentional non-adherence by psychological models. This suggests that these two types of non-adherence may be distinct from each other, and that participants are not simply reporting unintentional non-adherence as it is more socially acceptable.

The model combining both CSM and TPB variables provided the best fit for intentional non-adherence, explaining 46% of the variance. This combined model has been useful previously in predicting other health behaviours such as help seeking for breast symptoms (Hunter, Grunfeld, & Ramirez, 2003) and cervical cancer screening (Orbell, Hagger, Brown, & Tidy, 2006). Conceptualising these sets of beliefs together provides the best understanding of intentional non-adherence and is likely to be the best way to improve adherence. The results suggest that attitudes and perceptions around medication taking, as assessed by the TPB, and perceptions of breast cancer survivorship, as assessed by the CSM, are both central to understanding medication adherence. This highlights the importance of illness perceptions in breast cancer survivors and builds upon previous research using the CSM. Whilst women are no longer currently ill, their illness perceptions around survivorship and previous treatment are related to adherence. A recent review has found some evidence that interventions based on the CSM can improve adherence to a range of health behaviours, but concluded that more research was needed (Jones, Smith, & Llewellyn, 2015). Whilst intentional non-adherence is reported less often than unintentional non-adherence, this behaviour is likely to be harder to modify and it is therefore of great interest that the CSM/TPB provide good explanation of

this behaviour. Intentional non-adherence is also more likely to lead to discontinuation and therefore has strong clinical implications.

High risk of recurrence beliefs were associated with decreased odds of intentional non-adherence, probably because the fear of recurrence keeps women motivated to take tamoxifen. Stronger beliefs that psychological stress would cause a recurrence were associated with increased odds of non-adherence. If women endorse stress as a cause of recurrence then they may feel that there is no benefit in taking tamoxifen, as it does not control their stress levels. The necessity/concerns differential and tamoxifen consequences were significantly related to intentional non-adherence in the CSM model. This supports previous research suggesting that how people weigh up the necessity and concerns of treatment are related to whether or not they adhere (Horne & Weinman, 1999; Wileman et al., 2011). However the necessity/concerns differential and tamoxifen consequences were not significant once TPB variables were added, suggesting they may share variance with intention or PBC. Higher levels of PBC and intention were associated with decreased odds of intentional non-adherence. This is consistent with previous studies and theory (Bane et al., 2010) and suggests that interventions to improve PBC may help to improve adherence in this population. For example, implementation intentions, which are if-then goal plans where patients specify "I intend to do X at time Y in location Z", have been effective at increasing cervical cancer screening uptake (Sheeran & Orbell, 2000) and improving adherence in stroke survivors (O'Carroll, Chambers, Dennis, Sudlow, & Johnston, 2013).

Side-effects and distress were related to increased intentional non-adherence, but not when controlling for CSM and TPB variables. This is consistent with previous research which has found inconclusive evidence for the relationship between side-effects and non-adherence (Moon et al., 2017). Evidence suggests that women weigh up their necessity beliefs against their concerns when making decisions about taking tamoxifen (Fink, Gurwitz, Rakowski, Guadagnoli, & Silliman, 2004). If women have strong beliefs in the necessity of tamoxifen, they may continue to take it, regardless of side-effects. The results from the current study support this by showing that illness or treatment beliefs are stronger correlates of non-adherence than side-effects alone. This highlights the need to modify these psychological factors alongside side-effect management.

Women who had a double mastectomy were six times more likely to be intentionally non-adherent than women who did not have a double mastectomy, even after controlling for psychological variables. This may reflect a decision made by patients where they feel that tamoxifen is less necessary for them after removal of all breast tissue. A woman's choice to undergo a double mastectomy is a complex decision and is associated with a range of factors, such as treatment concerns (Molenaar et al., 2014) and fear of cancer recurrence (Nold et al., 2000). Therefore the

relationship between non-adherence and receipt of double mastectomy may also be driven by one of these factors.

The fact that the majority of clinical and demographic variables were not related to intentional non-adherence supports the findings of a recent review showing few consistent clinical or demographic predictors of non-adherence (Moon et al., 2017). This lack of clear factors on which to screen patients for non-adherence highlights the importance of investigating psychological factors as potential avenues for intervention. Results from this study suggest that utilising the key variables drawn from the models concurrently will give researchers and practitioners the best chance at improving adherence rates. Non-adherence appears to be related to perceptions around cancer as well as perceptions of control over medication taking. Therefore interventions which focus solely on one of these factors may miss out on key predictors of non-adherence.

However, whilst these psychological models provided good explanation for intentional non-adherence, adding CSM and TPB variables did not improve the prediction of unintentional non-adherence. Furthermore, study variables were only able to explain 17% of the variance in unintentional non-adherence, compared to 46% for intentional non-adherence. Therefore, more research is needed to improve understanding of unintentional non-adherence to tamoxifen. Some interventions have shown success at improving adherence using reminders or action plans (Brown, Sheeran & Reuber, 2009; O'Carroll et al., 2013; Webb & Sheeran, 2006), but as yet, no studies have attempted to improve unintentional non-adherence in women taking tamoxifen.

Whilst there were small correlations between medication beliefs and unintentional non-adherence, these relationships were not maintained in the regression analysis. This contrasts with previous research showing that unintentional non-adherence is predicted by medication beliefs (Gadkari & McHorney, 2012; Schüz et al., 2011). However, a recent study found that medication beliefs were associated with intentional but not unintentional non-adherence to HT (Brett et al., 2016), supporting the results of the current study. This suggests that unintentional non-adherence in this population may be influenced slightly by a patient's medication beliefs, but is much more likely to be due to forgetting or not establishing a good medication taking routine. This is further supported by the identification of unique predictors of both intentional and unintentional non-adherence.

Unintentional non-adherence was associated with demographic and clinical variables. Women who were white were less likely to be non-adherent than women who were not white, however the proportion of women of other ethnicities was small. Women who were older had higher odds of adherence, which has also been found in previous studies (Brett et al., 2016; Jacob Arriola et al., 2014; Kimmick et al., 2015) and may reflect the fact that young women may have difficulties

setting a routine around work or raising a family. Women who were employed had higher odds of non-adherence, independent of the effects of age. This supports findings of recent studies in HT adherence (Brett et al., 2016; Quinn, Fleming, & O'Sullivan, 2016) and may be due to practical problems, such as experience of side-effects in the workplace. Women with a longer time since tamoxifen initiation also had higher odds of non-adherence, which is supported by studies showing that non-adherence rates increase over time (Lee et al., 2014; Wu et al., 2012). These results help to identify women who are at higher risk of unintentional non-adherence, and who may need further support in taking their medication, such as women in the workforce or women from minority ethnic groups. However, more research on these relationships is necessary before any specific recommendations can be made for improving adherence in these subgroups, especially with regards to the results around ethnicity. Results indicate unique correlates of intentional and unintentional non-adherence in this population, suggesting interventions tailored to the type of non-adherence may be necessary.

Women in their first six months since prescription showed more favourable beliefs and perceptions towards tamoxifen than those later in the treatment pathway. They have higher intentions to take tamoxifen, lower distress scores, lower scores on tamoxifen consequences and attributed fewer side-effects to tamoxifen. These results suggest that it may be beneficial to intervene early before women's intention to take tamoxifen decreases and to help them successfully manage their side effects early on. Interestingly, many of the illness perceptions were not significantly different which suggests beliefs may not change over the course of treatment, which is contrary to the self-regulation proposed by the CSM. However, longitudinal research is needed to confirm this.

This study included a large nationwide sample and is, to the best of our knowledge, the first study to investigate correlates of tamoxifen non-adherence from the CSM and TPB. However, there were several limitations to the study. Adherence was measured by self-report, which may over-estimate adherence rates due to recall bias or socially-desirable answering. However, the MARS has been shown to correlate with more objective measures (O'Carroll et al., 2013), and non-adherence rates found in this study were comparable to studies using prescription refill rates (Partridge et al., 2003; Seneviratne et al., 2015). Taking less than 80% of prescribed doses is associated with decreased odds of survival in breast cancer patients (Hershman et al., 2011). Unfortunately we could not operationalise non-adherence in this way so it is unclear if the levels of non-adherence in this study are related to survival. Due to the cross-sectional design, it was also not possible to identify factors related to non-persistence. Future research should assess if the CSM and the TPB provide good explanation for non-persistence. We only tested illness and emotional representations within the CSM and missed other key elements of the model such as assessment of coping behaviours and appraisal. Although medication adherence could be seen as a coping behaviour used to control the

health threat, we did not measure the appraisal of non-adherence as a coping strategy. The study was cross-sectional and it therefore limits assumptions about causality. Future research should test these models in longitudinal studies. Finally, there may be some selection bias, as the response rate was 61% and patients who did not take part may be more likely to be non-adherent.

In spite of these limitations, the study makes an important contribution to the literature by showing that the CSM and TPB provide a useful framework for understanding intentional non-adherence to tamoxifen. It highlights the utility of these theories and demonstrates the importance of considering both theories concurrently when designing interventions. Results also highlight the extent of non-adherence in this population and suggest that unintentional and intentional non-adherence may be distinct behaviours with unique correlates. In particular, the study highlights the high proportion of unintentional non-adherence. As this behaviour was not explained well by the psychological models, there is a need to further understand this behaviour and to develop ways to improve unintentional non-adherence. Future research should confirm these findings in longitudinal studies and use the CSM and the TPB as a framework for designing interventions to improve adherence to tamoxifen.

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